July 1, 2003

Timothy Adams, Ph.D.
Technical Contact
The Flavor and Fragrance High Production Volume Consortia
Alicyclic Aldehyde Consortium
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Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 3 and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC) posted on the ChemRTK HPV Challenge Program Web site on February 25, 2003. I commend The Flavor and Fragrance High Production Volume Consortia Alicyclic Aldehyde Consortium for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The Flavor and Fragrance High Production Volume Consortia Alicyclic Aldehyde Consortium advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
3- and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC)

Summary of EPA Comments

The sponsor, the Alicyclic Aldehyde Consortium of the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries to EPA for HMPCC (CAS No. 31906-04-4) in December 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 25, 2003. The submission also contained robust summaries for related chemicals: 7-hydroxycitronellal, 4-isopropenyl-1-cyclohexene-1-carboxaldehyde, 2,4-dimethyl-3-cyclohexenecarboxaldehyde, 4-isopropenyl-1-cyclohexenecarbinol (perillyl alcohol) and 7-hydroxycitronellol.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. EPA agrees with the submitter's proposed testing for vapor pressure, octanol/water partition coefficient, and water solubility. The submitter needs to provide measured melting point data for HMPCC.

2. Environmental Fate. The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. Even though this chemical lacks hydroxyzable groups, the submitter needs to indicate this fact in robust summary format. EPA agrees with the submitter's proposed testing plan for biodegradation.

3. Health Effects. Adequate data are available for the acute, repeated-dose, and genetic toxicity endpoints for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposal to conduct testing for reproductive and developmental toxicity. The submitter needs to address deficiencies in the robust summaries.

4. Ecological Effects. The aquatic invertebrate toxicity data are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's plan to conduct acute toxicity tests on fish and algae.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the HMPCC Challenge Submission

General

The submission consists of data for a mixture of 3-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (30%) and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (70%). The data for structurally similar chemicals have been included to support the available information on this substance. The submission did not include CAS numbers for analogs.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

EPA agrees with the submitter's proposed testing for vapor pressure, octanol/water partition coefficient, and water solubility. The boiling point data are adequate for the purposes of the HPV Challenge Program.

Melting point. EPA agrees that because HMPCC is a mixture, the determination of a melting point for either the 3- or the 4-isomer is not relevant (and estimated melting points such as that provided in the test

plan are generally unreliable). The submitter needs to provide measured melting point data on the commercial mixture, following OECD TG 102 (as the commercial product is described as a viscous liquid at ambient temperature, the cited freezing point method may be appropriate).

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposed testing plan for biodegradation. When testing for biodegradation, EPA strongly recommends that the submitter follow OECD TG 301.

Stability in water. Although this chemical lacks hydroxyzable groups, the submitter needs to indicate this fact in robust summary format.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproduction/developmental toxicity).

Adequate data are available for the acute, repeated-dose, and genetic toxicity endpoints for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposal to conduct testing for reproductive and developmental toxicity. The submitter needs to address deficiencies in the robust summaries.

Repeated-Dose Toxicity. No data were submitted for HMPCC, but the reliance on analogs is justified by the metabolism data provided in section 2.5 of the test plan showing relatively rapid absorption of related substances and rapid excretion of metabolites. Of the studies submitted, NCI's 4-isopropenyl-1-cyclohexenecarbinol (perillyl alcohol) 90-day gavage study addresses this endpoint.

Reproductive/Developmental Toxicity. No data were submitted. EPA agrees with the submitter's plan for testing of HMPCC in a combined screening test for reproduction/developmental toxicity according to OECD TG 421. Although not provided by the submitter, published 14- or 28-day studies of perillyl alcohol showed testicular epithelial degeneration and irreversible testicular atrophy at 900 and 1000 mg/kg/day, respectively. These effects were not seen in the 90-day study in which the highest dose tested was 400 mg/kg/day. EPA suggests consideration of these data when setting up dose levels for the proposed reproduction/developmental toxicity study.

Ecological Effects (fish, invertebrates, and algae).

The submitted acute toxicity data for acute invertebrates are adequate for the purposes of the HPV Challenge program. EPA agrees with the submitter's plan to conduct OECD-compliant acute toxicity tests on fish and algae.

Specific Comments on the Robust Summaries

General comment

Throughout the robust summaries the title substance is HMPCC but often this is not the substance tested. To avoid confusion it is preferable to title each summary with the name of the substance tested and then to identify it as an analog of HMPCC. The summaries should also include CAS numbers for analogs.

Health Effects

Acute Toxicity. The following information is missing from the key study robust summary (Mallory, et al. 1982, Reliability Code 1): test substance purity, time of deaths at each dose, whether body weights were measured and any effects observed. There is a typographical error in the LD_{50} value field; the value is reported as "greater than 5,000 ml/kg bw" and the test was performed up to 6.0 ml/kg bw. The LD_{50} values needs to be reported as mg/kg bw (density of the test material is not provided in the submission).

Repeated-Dose Toxicity. A robust summary for an NCI 90-day gavage study for the analog perillyl alcohol lacks information on test material purity, statistical methods used, and method details such as hematology, clinical chemistry parameters, organ weights and organs evaluated histopathologically. The cited reference for this robust summary is incorrect. Journal of Cellular Biochemistry. 265, 137-148 should be Journal of Cellular Biochemistry. 26 S, 137-148.

Genetic Toxicity. The submitter needs to include information on test substance purity.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.